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Metronomic chemotherapy and radiotherapy as salvage treatment in refractory or relapsed pediatric solid tumours

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ABSTRACT

Background Metronomic chemotherapy (mctx) combined with radiation therapy (rt) is an emerging anticancer strategy. The aim of the present study was to assess the efficacy of mctx combined with rt as salvage treatment in children with refractory or relapsed solid malignancies.

Methods This prospective study enrolled patients with refractory or relapsed pediatric solid tumours from January 2013 to January 2015. Treatment consisted of 3–12 courses of mctx in all patients, followed by rt in patients who experienced local recurrence, distant metastases, or both. Each course of mctx consisted of oral celecoxib 100–400 mg twice daily (days 1–42), intravenous vinblastine 3 mg/m^2 weekly (weeks 1–6), oral cyclophosphamide 2.5 mg/m^2 daily (days 1–21), and oral methotrexate 15 mg/m^2 twice weekly (days 21–42). Statistical methods used were the log-rank test and binary logistic regression.

Results A favourable disease response (partial response or stable disease) was seen in 49 of 64 patients (76.6%), with mild acute toxicity occurring in 41 (64%). After a median follow-up of 14 months, 1-year overall survival was 62%. Pattern of disease relapse ($p < 0.0001$), time from initial treatment to relapse ($p = 0.0002$), and response to treatment ($p < 0.0001$) significantly affected survival. Age was the only factor that significantly correlated with treatment toxicity ($p = 0.002$; hazard ratio: 3.37; 95% confidence interval: 1.53 to 7.35)

Conclusions Combining mctx with rt resulted in a favourable response rate, minimal toxicity, and 62% 1-year overall survival in patients with heavily pretreated recurrent disease. Patients with localized late recurrence or disease progression are the most likely to benefit from this regimen.

Key Words Antiangiogenic therapy, palliative irradiation, treatment outcomes

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INTRODUCTION

Effectively treating recurrent pediatric solid malignancies is not an easy task. Most of these patients have a dismal prognosis and die within 2 years[1]. Conventional chemotherapy given at maximal tolerated doses results in disease control in pediatric cancer patients, but is frequently accompanied by side effects. Furthermore, treatment options for patients with disease progression after chemotherapy remain limited[2]. Chemotherapy regimens inhibit tumour angiogenesis, thus suppressing tumour vascularization[3,4]; however, long intervals between chemotherapy courses result in regrowth of the endothelial cells and further angiogenesis[5]. The antiangiogenic effects can be enhanced by shortening the period between chemotherapy cycles (continuous low-dose chemotherapy)[6], which also increases the proapoptotic effects of some chemotherapeutic drugs in tumour cells[7,8].

Low-dose chemotherapy administered continuously is called metronomic chemotherapy (mctx), and it is an option for the treatment of most cancer patients with disease progression[8]. Various chemotherapeutic drugs such as cyclophosphamide, methotrexate, and vinblastine that are cytotoxic to endothelial cells but not to non-endothelial cells are the mainstays of mctx[6,9].

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Low-dose cyclophosphamide has been documented to have a potential role in reducing the number and suppressing the function of regulatory T cells[10], resulting in tumour suppression and enhanced response[11]. In addition, low, non-cytotoxic concentrations of methotrexate and vinblastine promote maturation of dendritic cells and their antigen-presenting activity, and therefore support the development of antitumour immunity in tumour-bearing hosts[12]. Treatment of cells in culture with COX-2 inhibitor (celecoxib) is likely to lead to cell-cycle arrest[13] because of downregulation of the cyclin-dependent kinases that drive cell through the cell cycle[8]. That finding suggests that the cytotoxic effects of some chemotherapeutic agents might be potentiated when COX-2 inhibitors are added[11]. For the present study, we therefore chose a 4-agent MCTX regimen—celecoxib, cyclophosphamide, methotrexate, and vinblastine—with varying mechanisms of action (antiangiogenic, immunostimulatory, and apoptotic)[8], and we evaluated the efficacy of MCTX using that regimen followed by RT for treatment of patients with refractory or relapsed pediatric solid tumours who had been treated with standard initial chemotherapy at diagnosis and salvage treatment at time of disease relapse.

METHODS

Study Population

This prospective study was conducted at the pediatric oncology and radiotherapy departments of the South Egypt Cancer Institute, Assiut University, from January 2013 to January 2015, after registration of the study in the scientific research unit and approval by the institutional review board and ethics committee. The study enrolled pediatric patients 18 years of age or younger with relapsed or progressive solid tumours and adequate organ function, particularly defined as serum creatinine less than 1.5 mg/dL, total bilirubin 1.5 mg/dL or less, transaminases no more than twice the normal limit, hemoglobin 9.0 g/dL or greater, platelets 100,000/mm^3 or greater, white cell count 2000/mm^3 or greater, and absolute neutrophil count 1000/mm^3 or greater. Informed written consent was obtained from the parents of all patient before study enrolment. Patients with solid tumours that had recurred despite 2 or more regimens of therapy (given at initial diagnosis and for first relapse), were treated by MCTX, followed in most patients by RT to local and distant metastatic sites.

mCTx

Treatment consisted of 3 cycles of MCTX, each of 6 weeks' duration, followed by 1 week of rest. The chemotherapy consisted of celecoxib, cyclophosphamide, vinblastine, and methotrexate (Table I). A treatment duration of at least 21 weeks (3 cycles) was planned. Treatment beyond 21 weeks was continued in patients with either stable disease or a partial response.

Tumour size was evaluated using the method appropriate to the tumour site and size. The bi-dimensional measurements were made using ultrasonography or computed tomography imaging at study entry, after each MCTX cycle, and at study termination. Disease status was evaluated using World Health Organization response criteria:

TABLE I Drug and dosing schedule for metronomic chemotherapy

Drug	Schedule
Celecoxib	Oral, twice daily, days 1–42, by patient weight ■ <20 kg: 100 mg twice daily ■ 20–50 kg: 200 mg twice daily ■ >50 kg: 400 mg twice daily
Vinblastine	Intravenous, 3 mgm^2 weekly, weeks 1–6
Cyclophosphamide	Oral, 2.5 mg/kg daily, days 1–21
Methotrexate	Oral 15 mgm^2 twice weekly, days 21–42

- Progressive disease (PD): 25% increase in tumour size, or appearance of new lesions
- Stable disease (SD): neither partial response nor progression
- Partial response (PR): at least 50% decrease in tumour size
- Complete response: disappearance of all known lesions

Drug toxicity was evaluated using World Health Organization toxicity criteria[14]. Treatment was terminated by physician decision in the presence of disease progression or unacceptable toxicity.

RT Techniques

Patients who entered the study with isolated local relapse received MCTX followed by local RT (if not previously irradiated); those who entered with distant metastasis received MCTX followed by RT to the distant metastatic sites.

Patients with isolated local relapse were planned using 3-dimensional computed tomography for delineation of the gross target volume and critical structures, with the patient in supine position. Prone position was used in patients with back lesions. The clinical target volume included a 0.5-cm margin around the site of recurrent disease evident after the MCTX salvage treatment. The planning target volume included a 0.5-cm margin around clinical target volume. Conformal RT using 6 MV photon beams and customized blocks was given. The total radiation dose was assigned according to tumour type and site, prescribed to the isocentre. A total dose reduced by 13%, with a hypofractionated schedule (3 fractions per week), was given to younger patients who were anesthetized for immobilization during the radiation session. The clinical target volume had to be covered by the 95% isodose line. Patients with distant relapse received palliative RT at a dose of 30 Gy in 10 fractions.

Table II summarizes the treatments given by histopathologic tumour type.

Follow-Up Visits

At the end of treatment, patients were followed monthly during the study period by physical examination, routine laboratory investigations, and radiologic studies to assess response to treatment.

Statistical Methods

The study cut-off point was 1 January 2015. Overall survival (OS) was defined as the interval from enrolment (date of

TABLE II Summary of treatment by pathologic type

Histopathology	Pts (*n*)	Regimen		Relapse or progression type	Current salvage treatment					
		Initial	Salvage		Resection of local disease	Metronomic chemotherapy	Radiation		Median follow-up since initial	Description
							Local	Metastatic sites		
Rhabdomyosarcoma	14									
Low-risk	6	4–6 Courses of VACp chemotherapy, plus resection of local disease	4 Courses of ICE chemotherapy	Local recurrence	X	X	X		24 Months	Chemotherapy: 9 courses for 2 patients; 12 courses for 4 patients Radiation therapy: 41.4 Gy in 23 fractions to sites of local recurrence (*n*=6)
Intermediate- and high-risk	8	6 Courses of VACp chemotherapy, plus radiation therapy	6 Courses of ICE chemotherapy	Local recurrence, distant metastases[a]		X		X	18 Months	Chemotherapy: 3 courses for 3 patients; 9 courses for 5 patients Radiation therapy: 30 Gy in 10 fractions to sites of distant metastasis (bone or brain: *n*=5)
Neuroblastoma	13	7 Alternating courses of OPEC/OJEC chemotherapy, plus resection of local disease, plus radiotherapy	6 Courses of ICE chemotherapy	Progressive disease (*n*=4), distant metastases (*n*=9)		X		X	17 Months	Chemotherapy: 3 courses for 1 patient; 9 courses for 9 patients; 12 courses for 3 patients Radiation therapy: 30 Gy in 10 fractions to sites of distant metastasis (bone or brain: *n*=9)
Wilms tumour	10	All patients were treated according to the NWTSG protocol	6 Courses of ICE chemotherapy	Local recurrence, distant metastases[b]		X		X	21 Months	Chemotherapy: 12 courses for 5 patients; 9 courses for 5 patients Radiation therapy: 12 Gy in 8 fractions (lung metastases: *n*=4); 19.8 Gy in 11 fractions (liver metastases: *n*=2); 30 Gy in 10 fractions (bone metastases: *n*=4)
Brain tumour	9	Radiation therapy, plus weekly vincristine	3 Courses of ifosfamide–etoposide chemotherapy	Progressive disease					7 Months	Chemotherapy: 3 courses for all patients Radiation therapy: NA
Primitive neuroectodermal tumour	9	VACp alternating with ifosfamide–etoposide chemotherapy every 3 weeks for 54 weeks	Resection of local disease, plus 6 courses of ICE chemotherapy	Local recurrence (*n*=5) Local recurrence, distant metastases[c]		X	X	X	14 Months	Chemotherapy: 3 courses for 2 patients; 9 courses for 3 patients; 12 courses for 4 patients Radiation therapy: 54 Gy in 30 fractions to sites of local recurrence (*n*=5); 30 Gy in 10 fractions to sites of distance metastasis (bone or brain: *n*=2)

TABLE II Continued

Histopathology	Pts (*n*)	Regimen		Relapse or progression type	Current salvage treatment					
		Initial	Salvage		Resection of local disease	Metronomic chemotherapy	Radiation		Median follow-up since initial therapy	Description
							Local	Metastatic sites		
Germ-cell tumour	4	3–6 Courses of PEB chemotherapy, plus resection of local disease	3–6 Courses of VIP chemotherapy	Local recurrence		X	X		15 Months	Chemotherapy: 9 courses for 1 patient; 12 courses 3 patients Radiation therapy: 50.4 Gy in 28 fractions to sites of local recurrence (*n*=4)
Osteosarcoma	5	6 Courses of cisplatinum–doxorubicin chemotherapy	3 Courses of ifosfamide–etoposide chemotherapy	Local recurrence (*n*=1), distant metastases (*n*=4)		X			19 Months	Chemotherapy: 9 courses for 4 patients; 12 courses for 1 patient Radiation therapy: NA

[a] Sites: lung (*n* = 3), bone (*n* = 3), and brain (*n* = 2).
[b] Sites: lung (*n* = 4), bone (*n* = 4), and liver (*n* = 2).
[c] Sites: lung (*n*=2), bone (*n*=1), and brain (*n*=1).
VACp = vinblastine–doxorubicin–cyclophosphamide; ICE = ifosfamide–carboplatin–etoposide; OPEC = vincristine–cisplatin–etoposide–cyclophosphamide; OJEC = vincristine–carboplatin–etoposide–cyclophosphamide; NWTSG = National Wilms Tumor Study Group; NA = not applicable; PEB = cisplatinum–etoposide–bleomycin; VIP = vinblastine–ifosfamide–cisplatinum.

disease relapse or progression) to the date of death from any cause or to last follow-up. Univariate analysis by the log-rank test was used to examine differences in os rates. Binary logistic regression was used to assess correlations between toxicity and various prognostic factors.

RESULTS

Patient Characteristics

The study cohort included 64 patients [36 boys (56%), 28 girls (44%)] with a median age of 7 years (range: 3–17 years), of whom 20 (31%) were 5 years of age or younger, 25 (39%) were 6–11 years of age, and 19 (30%) 12–18 years of age. The most common diagnoses in the group were rhabdomyosarcoma (*n* = 14, 22%), neuroblastoma (*n* = 13, 20%), Wilms tumour (*n* = 10, 16%), brain tumour and peripheral primitive neuroectodermal tumour (*n* = 9 each, 14%). Most patients presented with disease relapse (*n* = 51, 80%); the remaining 13 presented with progressive disease (20%). In 16 patients, the relapse was local only; 35 patients presented with metastatic disease.

Of the 64 patients, 41 (64%) received RT—15 to local sites, and 26 to distant metastatic sites (Table II). The interval between initial treatment at diagnosis and enrolment of patients onto MCTX and RT ranged between 5 months and 36 months (median: 16 months). Early relapse (<18 months) or disease progression occurred in 39 patients (61%), and late relapse (≥18 months) occurred in 25 patients (39%).

Treatment Outcomes

After MCTX and RT, most patients (*n* = 49, 77%) experienced a favourable disease response; 22 (34%) experienced a PR, and 27 (42%) experienced SD. On the other hand, PD developed in 15 patients (23%). Acute toxicities (Table III)

TABLE III Treatment outcomes for patients with refractory or relapsed pediatric solid tumours

Variable	Value [*n* (%)]
Response to treatment	
Partial remission	22 (34.4)
Stable disease	27 (42.2)
Progressive disease	15 (23.4)
Treatment toxicity	
Hematologic toxicity	26 (40.6)
Anemia	16
Neutropenia	9
Anemia, neutropenia, thrombocytopenia	1
Nonhematologic toxicity	10 (15.6)
Peripheral neuritis	6
Chest infection	3
Mucositis	1
Combined toxicity	5 (7.8)
Anemia, mucositis	3
Anemia, chest infection	2
No toxicity	23 (36)

were mild: grade 1 hematologic toxicities (n = 26, 41%), nonhematologic toxicities (n = 10, **16%**), or a combination (n = 5, 8%). In 23 patients (36%), no toxicities were observed.

Anemia was the most common hematologic toxicity (n = 16), and peripheral neuropathy was the most common nonhematologic toxicity (n = 6). Binary logistic regression showed that age was the only factor that correlated significantly with toxicity [p = 0.002; hazard ratio (HR): 3.37; 95% confidence interval (CI): 1.53 to 7.35]. An analysis of toxicity by age group (Table IV) showed that grade 1 treatment-related toxicity occurred more often in the group 12–18 years of age (17 of 19 patients, **89%)** than in the group 5 years of age and younger (8 of 20 patients, 40%). The correlation between response to treatment and treatment-related toxicity (Pearson correlation) was not statistically significant (p = 0.124).

Survival Analysis

After a median follow-up of 14 months (range: 3–23 months), the 1-year OS rate was 62.3% (Figure 1). Univariate analysis showed 1-year OS rates of 20.5%, 83.2%, 64.2%, and 68.8% for patients with PD, isolated local recurrence, isolated metastatic disease, and combined disease relapse respectively (p = 0.0003). The 1-year OS was higher for patients who experienced a PR (82%) than for patients who experienced SD (70%) or PD (17%, p < 0.0001), and higher for those experiencing late relapse (84%) than for those experiencing early relapse or PD (48%, p = 0.0002). On the other hand, the 1-year OS rates were not significantly different by age group (p = 0.37), sex (p = 0.17; HR: 1.7; 95% CI: 0.799 to 3.65), pathologic type (p = 0.12), or treatment-related toxicity (p = 0.056; HR: 0.48; 95% CI: 0.23 to 1.02; Table V, Figures 2–5).

TABLE IV Presence or absence of toxicity by patient age group

Presence of toxicity	Age group			
	≤5 Years	6–11 Years	12–18 Years	Overall
Yes	8	16	17	41
No	12	9	2	23
TOTAL	20	25	19	64

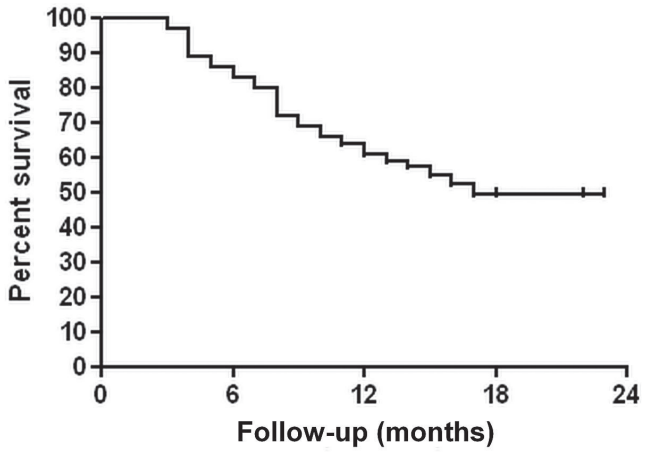

FIGURE 1 Overall survival in the patient cohort.

DISCUSSION

In the present study, we used a MCTX regimen consisting of 3 oral drugs (celecoxib, cyclophosphamide, methotrexate) and 1 intravenous drug (vinblastine) in conjunction with RT. The inclusion of celecoxib in the MCTX regimen was justified by reports from clinical trials suggesting some activity in pediatric malignancies when MCTX is used in conjunction with COX-2 inhibitors[15–20]. Vinorelbine[21] and etoposide[16] have been recommended for use in MCTX regimens based on their efficacy in pediatric patients with previously treated solid tumours. Because those two drugs were not available at our institute, we chose to use methotrexate and vinblastine, which have been included

TABLE V Univariate analysis of factors that might affect overall survival (OS)

Factor	1-Year OS (%)	*p* Value
Age group		
≤5 Years	75	0.37
6–11 Years	55	
12–18 Years	58.8	
Sex		
Girls	50	0.17
Boys	71.8	HR: 1.71
		95% CI: 0.799 to 3.645
Pathologic type		
Rhabdomyosarcoma	70.7	0.12
Neuroblastoma	53.8	
Wilms tumour	75	
Brain tumour	37.5	
Primitive neuroectodermal tumour	62.5	
Other	63.6	
Progression or relapse pattern		
Progression	20.5	0.0003
Isolated local recurrence	83.3	
Isolated distant metastasis	64.2	
Combined relapse	68.8	
Response to treatment		
Partial response	81.8	<0.0001
Stable disease	70.4	
Progressive disease	16.7	
Presence of toxicity		
Yes	51	0.056
No	82.6	HR:0.48
		95% CI: 0.23 to 1.02
Timing of relapse from initial Tx		
Early (<18 months)	48.4	0.0002
Late (≥18 months)	84	

HR = hazard ratio; CI = confidence interval; Tx = treatment.

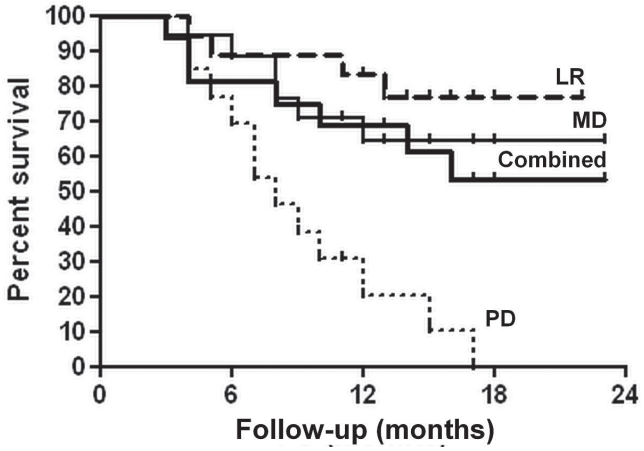

FIGURE 2 Overall patient survival by pattern of disease relapse. LR = local relapse; MD = metastatic disease; Combined = both relapse types; PD = progressive disease.

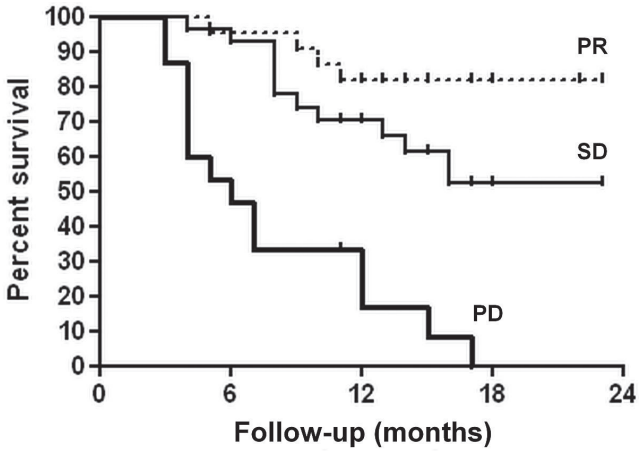

FIGURE 3 Overall patient survival by response to treatment. PR = partial response; SD = stable disease; PD = progressive disease.

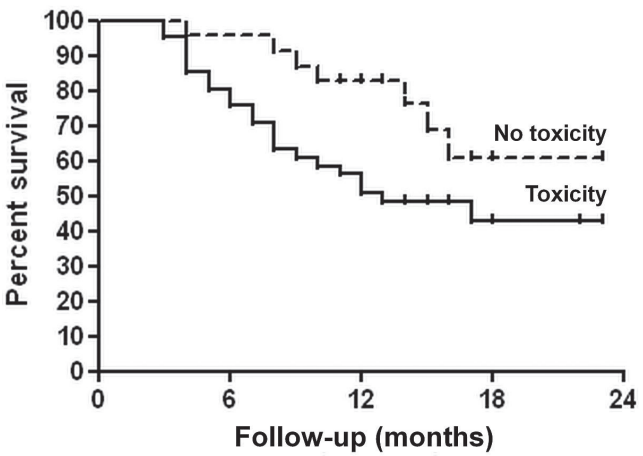

FIGURE 4 Overall patient survival by treatment-related toxicity.

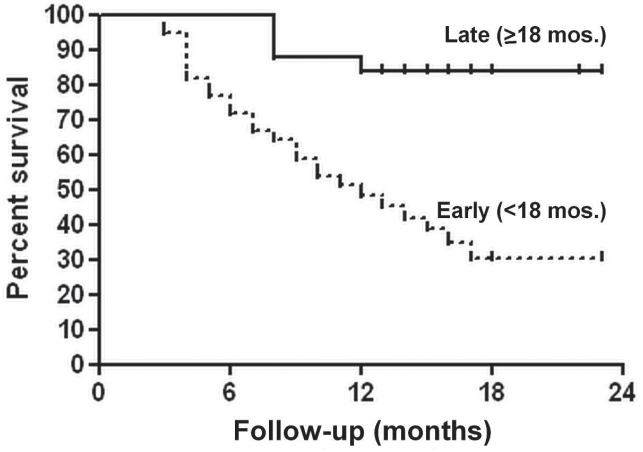

FIGURE 5 Overall patient survival by relapse (early or late) after treatment received at initial diagnosis.

in other MCTX studies[8,18]. The celecoxib–vinblastine–cyclophosphamide–methotrexate drug regimen used in the present study is likely to have various mechanisms of antiangiogenesis without overlapping toxicities, resulting in inhibition of various steps in the tumour neovascularization process[12,18].

A response, defined as PR or SD after 6 months, was achieved in 77% of the study patients (34% PR, 42% SD). The higher rate of SD compared with PR in the present study can possibly be explained on the grounds that, in recurrent tumours, antiangiogenic agents inhibit neovascularization (resulting in SD) rather than established vasculature (which would result in shrinkage and PR). However, for most cancer patients who have already been treated in the first and second chemotherapy lines, and for whom no other efficient salvage therapy is anticipated, stopping tumour growth can be considered a favourable outcome[16].

Univariate analysis showed favourable 1-year OS rates for patients with isolated local recurrence and with late relapse. The encouraging response rate and the relatively favourable OS rate (1-year OS: 62%) in our cohort might be explained by preclinical and clinical findings of a direct relationship between RT and tumour vasculature. The blood vessels in tumours are dilated and tortuous, leading to non-uniform distribution of chemotherapeutic drugs and oxygen[22,23]. Antiangiogenic treatment normalizes tumour vasculature and oxygenation[24]. A combination of RT and MCTX can lead to better clinical efficacy in various cancers, because antiangiogenic therapy increases oxygenation and radiosensitivity[23,25], augmenting radiation efficacy[26]. Our findings might confirm a study reported by Sterba *et al.*[15], who showed encouraging results for RT combined with metronomic temozolomide in children with medulloblastoma.

The drug regimen used in the current study was well tolerated in our pretreated patients; it produced only mild acute toxicities and did not result in treatment interruption. No patient required blood transfusion or growth factor administration. More than one third of the patients (n = 23, 36%) showed no toxicities. The use of low intravenous

doses of vinblastine, with oral administration of the other 3 drugs in the regimen at home, was convenient for the prolonged and frequent dosing. Those findings are confirmed by other studies[16–18] reporting that chronic administration of low-dose chemotherapy results in less toxicity and better quality of life in patients with advanced or relapsed cancer.

Binary logistic regression showed that age was significantly correlated with treatment toxicity ($p = 0.002$; HR: 3.37; 95% CI: 1.53 to 7.35), with grade 1 toxicity being present in 89% (17 of 19) of patients 12–18 years of age and in 40% (8 of 20) of patients 5 years of age or younger. That result might be explained by the fact that cells of normal tissues in younger children are dividing and multiplying more rapidly than they are in older children, resulting in faster recovery from MCTX-related toxicities. That hypothesis accords with a report from Rask *et al.*[27], who found that increasing age was a significant risk factor for chemotherapy-related toxicity.

CONCLUSIONS

In children with relapsed pediatric solid tumours, especially those with isolated local relapse and late relapse, MCTX combined with RT resulted in a favourable response rate with minimal toxicity. The 1-year OS rate was 62%. Although the principal target of MCTX is tumour neovasculature, an MCTX regimen can directly attack tumour-cell proliferation earlier in the disease process. Future studies are recommended to evaluate the efficacy of MCTX as first salvage treatment in patients with relapsed pediatric solid tumours, especially those with localized disease and late relapse.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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